REMARKS

Consideration of this response is respectfully requested, as no new search would be required and it would not place undue burden on the Examiner.

Reconsideration and allowance are respectfully requested.

Claims 6, 8, 9, and 11 are pending and claims 6, 8, and 9 are at issue. In this response, claim 6 has been amended to include "a pharmaceutically acceptable carrier or excipient". Support for this amendment can be found in the specification as filed (see, e.g., page 15 of the specification, which describes the use of water and, optionally, buffering and stabilizing agents.) No new matter is added.

Claims 6, 8, and 9 have been rejected under 35 U.S.C. § 103 as unpatentable over Drejer et al., *Diabetes* 40:1488 (1991), in view of the specification (pages 9-11 and Table 1), with or without Bakaysa et al., US Patent No. 5,474,978, De Filippis, US Patent No. 5,461,031, or Balschmidt, WO 95/00550.. The Examiner contends that Drejer et al. discloses compositions comprising Asp-B25 human insulin and provides "explicit motivation" to formulate pharmaceutical compositions comprising Asp-B25 human insulin, "especially for investigations involving the determination of these analogs for their **in vivo activity as fast-acting analogues**" (Office Action at Page 5, emphasis provided by Examiner).. This rejection is respectfully traversed.

The present invention is based on the finding that administration of *hormonally inactive* insulin analogues is effective in preventing the onset of autoimmune diabetes. Drejer et al. is completely silent with respect to any possible therapeutic use of insulin analogues that are hormonally inactive. Asp-B25 is not a fast-acting insulin analogue; to the contrary, Asp-B25 exhibits only minimal insulin activity. The Examiner's emphasis (see above) is therefore misplaced, as the present invention does *not* encompass the use of fast-acting insulin analogues to treat hyperglycemia. It is noteworthy that Table 1 illustrates that none of the insulin analogues of claim 6 exhibits even 10% of the activity of human insulin. Thus, it is not understood on what basis the Examiner contends that Drejer et al. could provide motivation for one of ordinary skill in the art to formulate inactive insulin analogues for therapeutic use, when they would not be effective as hypoglycemic agents (the only therapeutic use to which Drejer et al. relates.) To the contrary, Drejer et al. would only discourage one of ordinary skill in the art from preparing or using the presently claimed pharmaceutical formulations.

None of the secondary references remedies the deficiencies of Drejer et al. Bakaysa et al. and de Filippis both relate to insulin lispro, which is a fast-acting analogue. Similarly, Balschmidt et al. relates to other fast-acting insulin analogues (exemplified by Asp B28 insulin). None of these fast-acting (hormonally active) analogues are encompassed by the present claims, and, in fact, none of these could be used in practicing the present invention because of their ability to lower blood glucose. (See, e.g., present specification at page 8, lines 26-38).

In summary, none of the cited references, either singly or in combination, provides any hint or suggestion, any motivation, or any reasonable expectation of achieving tolerization to autoimmune diabetes using a hormonally inactive insulin analogue.

On this basis, it is respectfully submitted that the present invention is non-obvious over the cited references and that this rejection should be withdrawn.

In view of the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

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Reza Green, Reg. No. 38,475
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

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